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(54) Title: THROMBORESISTANT COATING MADE OF ACRYLIC POLYMER

(57) Abstract

An acrylic polymer composition for raising the thromboresistance of a surface on which it is deposited comprising as follows (in parts by weight): Acrylic copolymer emulsion dry weight 100 parts, anti-coagulant 0-60 parts, wax emulsion dry weight 0-30 parts, water 100-700 parts.

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THROMBORESISTANT COATING MADE OF ACRYLIC POLYMER

The present invention relates to a method of coating a surface to render it thromboresistant.

Thromboresistance is important for medical devices exposed to blood flow for an extended length of time. Failure to render the surface of such a device thromboresistant can result in formation of a thrombosis, which can lodge in a life threatening position in a patient.

A number of factors can increase the thromboresistance of a surface, but no one single factor appears to ensure complete thromboresistance.

In particular, surface smoothness, with resultant deterrence for air to be retained at the surface is a significant factor. Blood coagulates in the presence of air. In addition increase in surface energy to a certain extent can improve thromboresistance.

Anti-coagulants are well known and can be deposited on a surface to improve its thromboresistance.

The object of the present invention is to provide improved thromboresistance of a surface of a medical device.

According to one aspect of my invention, there is provided a method of raising the thromboresistance of a surface of a medical device by depositing on it a non-toxic acrylic polymer composition.

According to another aspect of the invention there is provided a non-toxic acrylic polymer composition for raising the thromboresistance of a surface on which it is deposited.

Preferably the composition is deposited by flowing the composition in a water based emulsion of it over the surface. Where the shape of the device lends itself, the flowing can be achieved by pumping the emulsion through it. This has particular advantage where the medical device is of complex shape, since it enables interstices which the blood can readily reach in use of the device to be treated. Alternatively, the medical device can be dipped into the emulsion. The process can be completed by blowing warm air through or over the device. This removes the water and any residual low molecular weight volatiles, from the emulsion, leaving the acrylic polymer composition deposited on the surface.

Advantageously, the acrylic polymer is provided as a copolymer.

In certain embodiments, better thromboresistance can be provided by incorporation of a water soluble anti-coagulant into the emulsion. The anti-coagulant is deposited with the acrylic polymer. It acts to discourage initiation of coagulation on the surface. Suitably the anti-coagulant can be heparin or heparin derivatives, trisodium citrate, citric acid or hirudin or hirudin derivatives.

Additionally or alternatively, a hydrophobic material can be incorporated in the emulsion. Suitably an emulsifiable wax can be used. It is deposited with the acrylic polymer and by its surface energy discourages any deposit from blood on the surface having the composition on it. Where both anti-coagulant and hydrophobic materials are incorporated, it is believed that the latter slows leaching of the former from the composition.

To help understanding of the invention, two specific embodiments thereof will now be described by way of example and with reference to the accompanying drawings, in which:

Figure 1 is a diagrammatic view of a blood heat exchanger being treated in a first step in depositing an acrylic copolymer composition in accordance with the invention;

Figure 2 is a similar view of a second step in the treatment of the heat exchanger; and

Figure 3 is a similar view of other medical devices being treated in accordance with the invention.

The blood temperature regulation heat exchanger 1 shown in Figure 1 has a blood inlet 2 and a blood outlet 3. Internally, it has a highly contoured heat exchange element with an extensive surface area and small gaps between its parts. The exact structure is not shown since it is its general nature, as just described, which is relevant. However the materials of its construction, namely stainless steel, polycarbonate and potting compounds should be noted.

Figure 1 shows a pump 4 connected by pipes 5, 6 to the inlet 2 and outlet 3 of the heat exchanger via a vat 7 of emulsified thromboresistant composition described below. In a first step of treatment of the blood side of the heat exchanger, the composition is pumped through it, allowing the emulsified components of the composition to deposit over the entire internal wetted surface of the heat exchanger.

After a suitable length of time for the composition to build up, typically 20 minutes, the pump is stopped and the pipes 5, 6 removed. After the remaining liquid has drained from it, the exchanger has a drying air duct 11 connected to the inlet 2 and a blower 12 blows air through the exchanger until the composition has dried, see Figure 2. A moisture trap 13 and an exhaust extraction fan 14 are fitted to the outlet of the heat exchanger. After drying, the inlet and outlet are sealed until the device is used.

As mentioned above, the heat exchanger is made of a variety of dissimilar materials. The composition of the emulsified thromboresistant composition is as follows (in parts by weight):

Acrylic copolymer emulsion	
typically Texicryl TD 6213	100 parts
Anti-coagulant	
typically trisodium citrate	0-30 parts
Wax emulsion	0-50 parts

Water	0-150 parts.

Texicryl is a product from Scott Bader Co. Ltd., Wellingborough, England.

Tests have shown that this composition deposits on all the materials of the heat exchanger and renders them all thromboresistant for the periods of time for which the heat exchanger is in use, which can be up to 6 hours or so.

The composition described above includes a quantity of water of 0-150 parts by weight. However, both the polymer emulsion and the wax emulsion include water, and thus the total water content of the composition may exceed the 150 parts as stated above. Typically the polymer emulsion will contain 50% water by weight, but could contain from 20% to 80 %, and the wax emulsion will typically contain 80% water, (see later), but could contain from 30% to 90% water. Thus the composition is composed as follows (in parts by weight):

Acrylic copolymer	
dry weight	100 parts
Anticoagulant	0-60 parts
Wax	
dry weight	0-30 parts
Water	100-700 parts.

Figure 3 shows an alternative method of treatment, useful for elongate devices 21, such as stents and catheters. These are suspended from hooks 22 above a vat 23 of emulsified thromboresistant composition. The hooks are ganged together and can be lowered towards the vat, for immersion of the devices in the composition. They are successively lowered and raised until the composition has built on the surface of the devices to a sufficient extent. Where it is critical that all surfaces are completely covered including the point of connection to the hooks - as in a stent as opposed to a catheter or wound drain having an end left outside the body - the devices can be upended half way through the treatment process. As with the heat exchanger, the final step in the treatment is the drying of the composition deposited on the devices.

Stents are usually of stainless steel and can be treated with the same composition as the heat exchanger.

Wound drainage catheters are usually of polyvinylchloride PVC, polyurethane PU, or silicone material. The latter two materials are known to be more thromboresistant. Tests have shown the thromboresistance of PVC catheters can be improved to the level of those of PU catheters by treatment with a similar composition to that used for the heat exchanger, without the wax emulsion.

To improve the lubricity of the catheters, to ease their insertion and withdrawal, treatment with a further composition by overcoating with a hydrogel coating on top of the thromboresistant coating results in an equally improved thromboresistance.

The hydrogel coating can be an aqueous solution of poly(hydroxy ethyl methacrylate) (HEMA), polyvinylalcohol (PVOH), poly(N-vinyl-2-pyrrolidone) interpolymer (PVP) or poly(ethylene oxide) (PEO) as well as suitable hydrocolloids.

Texicryl TD 6213 (a Scott Bader trade name) is a styrene-acrylate copolymer emulsion. It is anticipated that other acrylic compositions will be effective, in particular copolymers based on:

(meth)acrylic esters

styrene and acrylic acid esters

styrene and (meth)acrylic esters.

As an alternative to Texicryl TD 6213 other suitable polymers include Revacryl 100, 123, 143, 612, all products of Harlow Chemical Co. Ltd., Harlow, England.

Texicryl TD 6213 is a copolymer emulsion, formed by emulsion polymerisation. The copolymer has a styrene butyl acrylate backbone, with a glass transition temperature of -12°C. Alternatively styrene-2-ethyl hexyl acrylate can be

used. The emulsion stabilising system utilises an alkali soluble copolymer with carboxylic acid functionality. This is used to achieve high resistance to water attack. Ammonia is used to solubilise the copolymer which, on drying, leaves an insoluble ammonium salt. The carboxylic acid functionality gives good compatibility (and potentially chemical bonding) with the styrene butyl acrylate, the main polymer, rendering the whole system resistant to re-emulsification.

It should be noted that not all acrylic polymers are suitable. In particular they should be non-toxic. For devices having a long life in use they should be resistant to attack by body fluids.

The wax emulsion is preferably based on either beeswax or paraffin to avoid toxicological problems. The composition of a preferred paraffin wax emulsion is as follows (in parts by weight):

Paraffin Wax BP 52°C solidification point (CAS No 8002-74-2)	10-30 parts
Glycosperse TS 20 POE(20) Sorbitan tristearate ethoxylated (CAS No 9005-71-4)	0-5 parts
Glycosperse O 20 Polysorbate 80 or POE(20) Sorbitan monooleate ethoxylated (CAS No 9005-65-6)	0-5 parts
Water	70-90 parts

Glycosperse (a trade mark of Lonza Inc., Fair Lawn, New Jersey) is an ethoxylated non-ionic surfactant.

The composition of a preferred beeswax emulsion is as follows (in parts by weight):

Yellow Beeswax BP

(melting point 61-65°C)	
(CAS No 8012-89-3)	10-30 parts
Glycosperse TS 20	
POE(20) Sorbitan tristearate	0-5 parts
Glycosperse O 20	
POE(20) Sorbitan monooleate	0-5 parts
Water	70-90 parts

Advantages of the invention can include:

i) No unusual cleaning of the medical devices (beyond that dictated by their medical use) prior to treatment in accordance with the invention is thought to be necessary;

ii) The compositions and coating processes involved are low cost;

iii) Use of devices treated with the coating is anticipated to result in improvements in patient safety, care and recovery rates;

iv) Use of an aqueous emulsion avoids the use of solvents which are expensive and/or awkward to dispose of and avoids involvement in VOC regulations.

Aside from being applicable to a wide range of substrates, the compositions of the invention are flexible, allowing their use on devices such as stents which are subject to continual flexure.

Claims:

1. A method of raising the thromboresistance of a surface of a medical device by depositing on it a non-toxic acrylic polymer composition.

2. A method as claimed in claim 1, wherein the composition is deposited by flowing the composition in a water based emulsion of it over the surface.

3. A method as claimed in claim 1 or claim 2, wherein the composition is pumped through the device.

4. A method as claimed in claim 1 or claim 2, wherein the composition is deposited by dipping into the emulsion.

5. A method as claimed in any previous claim, wherein the process is completed by blowing warm air through or over the device to remove the water or any residual low molecular weight volatiles from the emulsion, leaving the acrylic polymer composition deposited on the surface.

6. A method as claimed in any previous claim, wherein the devices treated are made from materials including at least one of stainless steel, polycarbonate, potting compounds, polyvinylchoride.

7. A method as claimed in any previous claim, wherein anti-coagulant is deposited with the acrylic polymer.

8. A method as claimed in any previous claim, wherein hydrophobic material is deposited onto the surface with the acrylic polymer.

9. A method as claimed in any previous claim, wherein a hydrogel is deposited over the acrylic polymer composition.

10. A method as claimed in claim 9, wherein the hydrogel is an aqueous solution of poly(hydroxy ethyl methacrylate), or polyvinylalcohol, or poly(N-vinyl-2-pyrrolidone) interpolymer, or poly(ethylene oxide) or a hydrocolloid.

11. A method substantially as hereinbefore described with reference to Figures 1 and 2, or Figure 3 of the accompanying drawings.

12. A composition for raising the thromboresistance of a surface on which it is deposited, the composition being a non-toxic acrylic polymer composition.

13. A composition as claimed in claim 12, wherein the acrylic polymer is provided as a copolymer.

14. A composition as claimed in claim 12 or claim 13, further containing a water soluble anti-coagulant in the emulsion.

15. A composition as claimed in claim 14, wherein the anti-coagulant is heparin or heparin derivatives, trisodium citrate, citric acid or hirudin or hirudin derivatives.

16. A composition as claimed in any one of claims 12 to 15, wherein a hydrophobic material is incorporated in the emulsion.

17. A composition as claimed in claim 16, wherein the hydrophobic material is emulsifiable wax.

18. A composition as claimed in claim 17, wherein the composition is as follows:-

Acrylic copolymer emulsion	
dry weight	100 parts
Anti-coagulant	0-60 parts
Wax emulsion	
dry weight	0-30 parts
Water	100-700 parts

19. A composition as claimed in any one of claims 12 to 18, wherein the acrylic copolymer emulsion is Texicryl TD 6213 in which the copolymer has a styrene butyl acrylate backbone.

20. A composition as claimed in any one of claims 12 to 18, wherein the acrylic copolymer emulsion has a styrene-2-ethyl hexyl acrylate backbone.

21. A composition as claimed in any one of claims 12 to 20, wherein the copolymer is alkali soluble.

22. A composition as claimed in any one of claims 12 to 18, wherein the acrylic copolymer emulsion is Revacryl 100, 123 143 or 612.

23. A composition as claimed in any one of claims 12 to 18, wherein the acrylic composition includes copolymers based on:

(meth)acrylic esters

styrene and acrylic acid esters

styrene and (meth)acrylic esters.

24. A composition as claimed in claim 17, or any one of claims 18 to 23 as appendant to claim 17, wherein the wax emulsion composition is as follows (in parts by weight):

Paraffin Wax BP	
(52°C solidification point) (CAS No 8002-74-2)	10-30 parts

Glycosperse TS 20

POE(20) Sorbitan tristearate ethoxylated

(CAS No 9005-71-4) 0-5 parts

Glycosperse O 20

Polysorbate 80 or

POE(20) Sorbitan monooleate ethoxylated

(CAS No 9005-65-6) 0-5 parts

Water 70-90 parts

25. A composition as claimed in claim 17, or any one of claims 18 to 23 as appendant to claim 17, wherein the wax emulsion composition is as follows (in parts by weight):

Yellow Beeswax BP

(melting point 61-65°C) (CAS No 8012-89-3) 10-30 parts

Glycosperse TS 20

POE(20) Sorbitan tristearate 0-5 parts

Glycosperse O 20

POE(20) Sorbitan monooleate 0-5 parts

Water 70-90 parts.

26. A medical device treated in accordance with the method as claimed in any one of claims 1 to 11, with the composition as claimed in any one of claims 12 to 25.

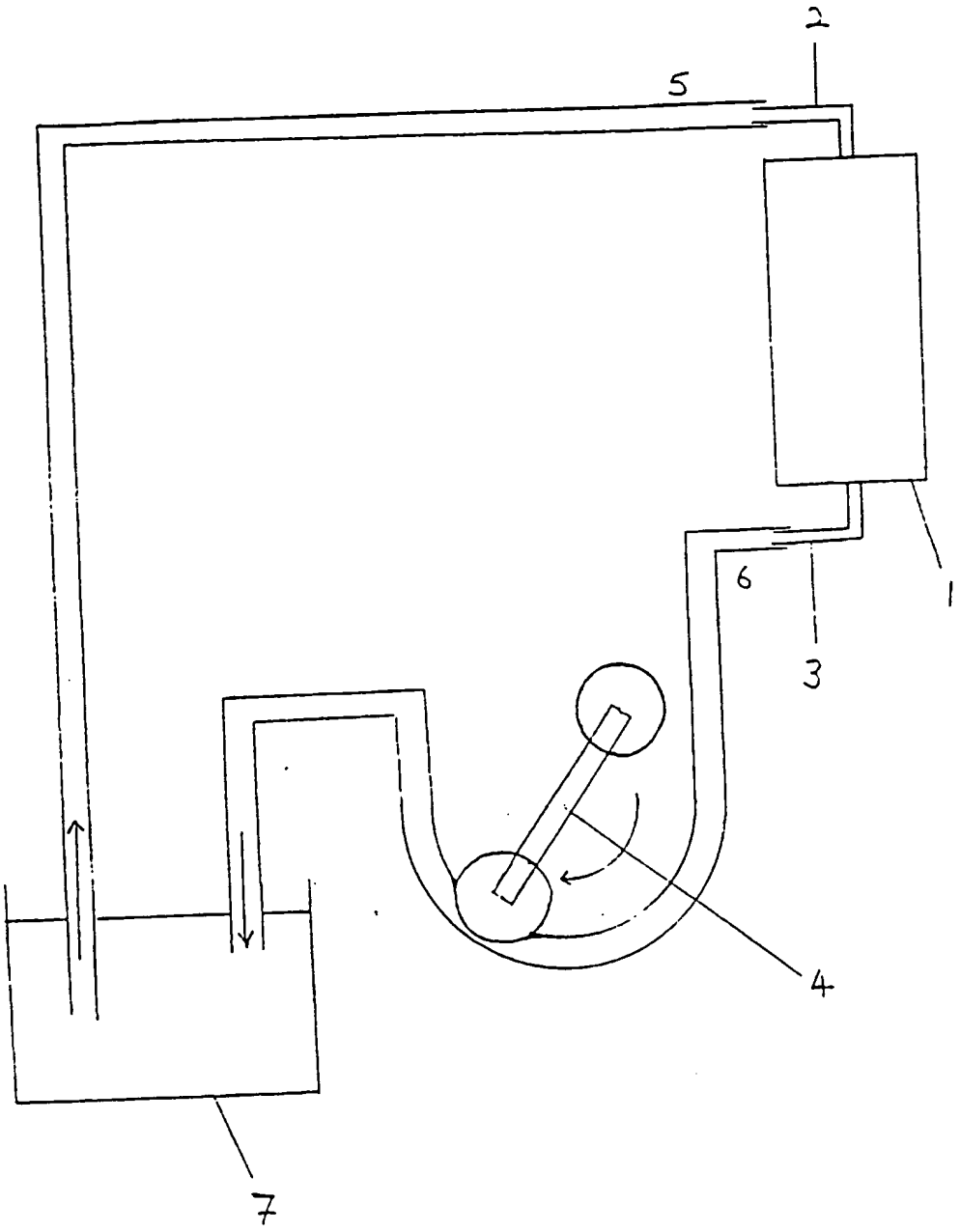

FIGURE 1

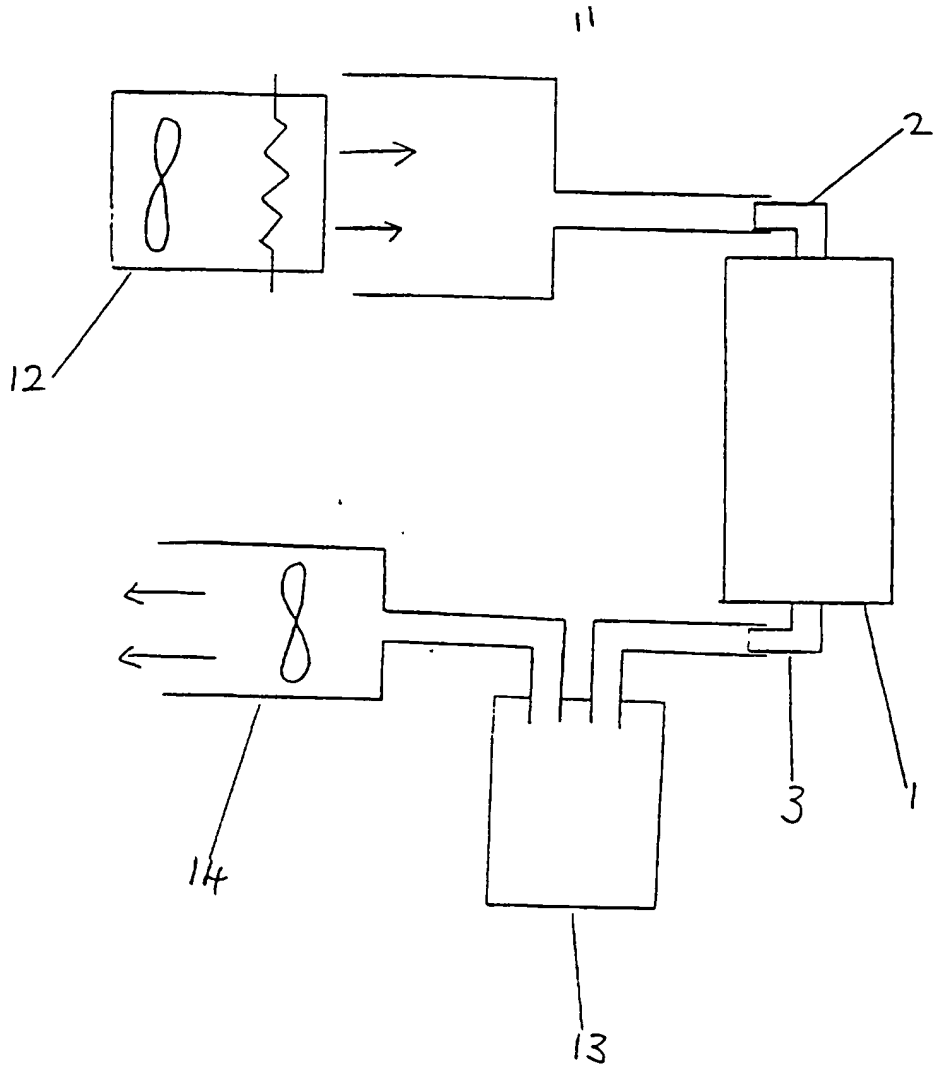

FIGURE 2

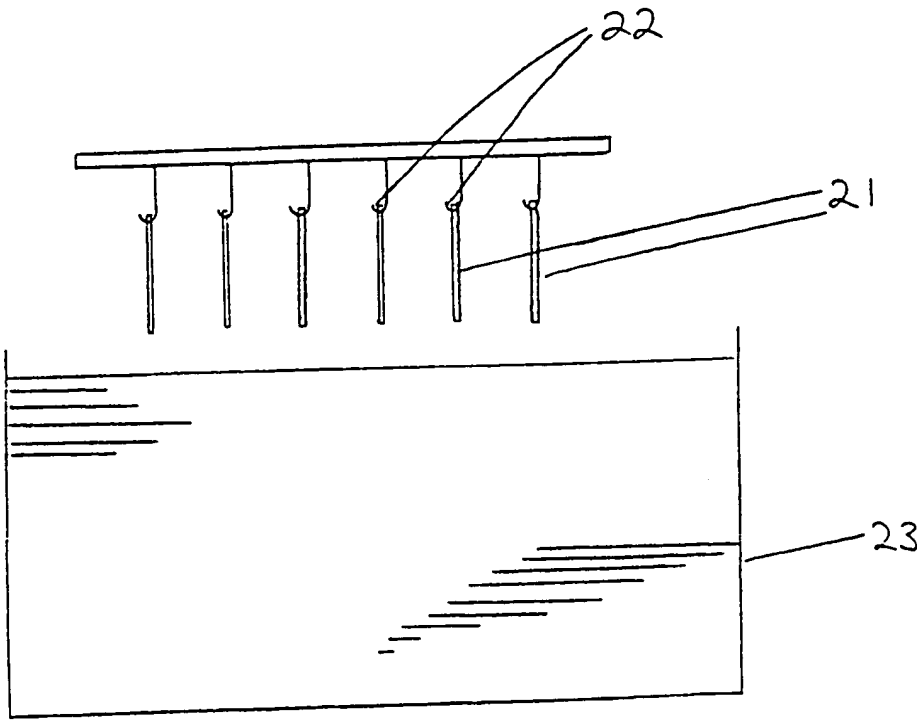

FIGURE 3

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/GB 97/01886

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L33/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
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Y	see page 3, line 35 - line 45 see page 4, line 2 - line 11 see claims 1-4,11,12,18,19,22 ---	8,16-18,22,23
Y	EP 0 003 389 A (BRITISH PETROLEUM CO) 8 August 1979 see abstract see page 2, line 1 - line 14 see page 3, line 10 - line 21 see page 3, line 28 - line 33 see page 4, line 12 - line 23 see example 1 --- -/--	8,16-18,22,23

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 November 1997	05/12/1997

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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